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Proposed Registration Decision PRD2016-18

Tea Tree Oil

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Overview

Proposed Registration Decision for Tea Tree Oil

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Tea Tree Oil Technical and Timorex Gold, containing the technical grade active ingredient tea tree oil, to control powdery mildew on greenhouse pepper, tomato, cucumber and grape, suppress powdery mildew on strawberry, suppress downy mildew on grape and greenhouse cucumber, and suppress late blight on greenhouse tomato.

Tea Tree Oil Technical (Registration Number 30909) and Timorex Gold (Registration Number 30910) are conditionally registered in Canada. The detailed review for Tea Tree Oil Technical and Timorex Gold can be found in Evaluation Report ERC2014-01, *Tea Tree Oil*. Since the original applications, amendments have been made to the Timorex Gold label to add field peppers, blueberries, raspberries, and potatoes. The current applications were submitted to convert Tea Tree Oil Technical and Timorex Gold from conditional registration to full registration.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Tea Tree Oil Technical and Timorex Gold.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "... the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

Before making a final registration decision on tea tree oil, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on tea tree oil, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Tea Tree Oil?

Tea tree oil is an extract from a cultivated tree native to Australia, New Zealand and Southeast Asia. It contains several organic compounds with anti-fungal properties and will control or suppress certain fungal diseases present in Canada when applied in the end-use product, Timorex Gold.

Health Considerations

Can Approved Uses of Tea Tree Oil Affect Human Health?

Tea Tree Oil is unlikely to affect human health when used according to label directions.

Potential exposure to tea tree oil may occur through the diet (food and water) or when handing and applying the end-use product, Timorex Gold. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Tea tree oil is slightly acutely toxic via the oral route and of low acute toxicity via the dermal and inhalation routes. It is a severe eye and skin irritant, and is considered to be a skin sensitizer. Although tea tree oil has low acute inhalation toxicity, because of its eye and skin irritancy, it is considered to be a potential respiratory irritant if inhaled. Consequently, appropriate hazard signal words are required on the label.

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

The end-use product, Timorex Gold, has low acute toxicity via the oral, dermal, and inhalation routes of exposure. It is moderately irritating to the eyes and skin and is considered to be a skin sensitizer. Because of its eye and skin irritancy, it is considered to be a potential respiratory irritant if inhaled. Based on these characteristics, appropriate hazard signal words are required on the label.

Animal toxicity tests provided, as well as information from the published scientific literature, were assessed for the potential of tea tree oil to cause short-term toxicity, developmental effects, genotoxicity, and various other effects. Tea tree oil was determined to not be genotoxic, and there was no indication that the young were more sensitive than the adult animal. The risk assessment protects against these, and any other potential effects, by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Dietary risks from food and drinking water are not expected to be of concern given the low toxicity and dietary and drinking water exposures to tea tree oil. The major components of tea tree oil (monoterpenes, sesquiterpenes, and related alcohols) are volatile, and after application, tea tree oil is expected to substantially volatilize with low residence times on plants and soil. In submitted residue trials, the levels of tea tree oil components on treated crops were less than the limit of quantification 48 hours after the application of Timorex Gold. Accordingly, the pre-harvest interval of two days for the end-use product is expected to further encourage the dissipation of any tea tree oil residues prior to harvesting treated crops. In addition, based on information from the United States Food and Drug Administration, consumers are already exposed to low levels of tea tree oil components as they are approved for use as food flavouring substances, in sanitizing solutions for food-processing equipment, and in coatings on food contact surfaces. Consequently, the specification of a maximum residue limit for tea tree oil under the *Pest Control Products Act* is not required. Because tea tree oil and its components are volatile, have low water solubility, have low residence times in environmental media, and the end-use product has label directions against application to water or contaminating water when cleaning equipment, there is not likely to be any significant contamination of ground or surface water sources of drinking water.

Risks in Residential and Other Non-Occupational Environments

Non-occupational risks from bystander exposure are not of concern.

Risks to bystanders from commercial applications of Timorex Gold are not expected to be of concern due to the low toxicity of tea tree oil and the low potential for bystander exposure when the end-use product is applied according to label directions.

Occupational Risks from Handling Tea Tree Oil

Occupational risks are not of concern when used according to label directions.

There is a potential for dermal and inhalation occupational exposures to tea tree oil during mixing, loading, application, clean-ups, and repairs when using Timorex Gold. There is a similar potential for exposure if workers enter treated areas before sprays have dried. To minimize such exposure, the label for Timorex Gold includes precautionary, personal protective equipment, and hygiene statements, as well as a four-hour restricted-entry interval (REI) and a requirement for greenhouse vents to be open and fans operational during the REI. Taking into consideration the precautionary measures, label statements, and the REI, occupational risks from tea tree oil are not expected to be of concern.

Environmental Considerations

What Happens When Tea Tree Oil Is Introduced Into the Environment?

When Tea Tree Oil Technical and Timorex Gold are used according to label instructions, tea tree oil is not expected to pose risks of concern to the environment.

Tea Tree Oil Technical and its related end-use product, Timorex Gold, will enter the environment when applied as a fungicide, using field and airblast sprayers, on various field and greenhouse crops. It can enter soil directly at the time of application and it can enter aquatic environments directly through spray drift or via run-off from the treated field. Tea tree oil is composed of several chemicals that evaporate easily at normal temperatures and are all expected to be found in air within the first 24 hours after application of Timorex Gold. These chemicals are quickly broken down and are, therefore, expected to be short-lived in the environment (soil, air and water) and are not expected to be found in groundwater. Direct contact with the spray or drifting spray droplets may, however, be possible for certain non-target organisms for a short period of time after application of Timorex Gold. Tea tree oil is toxic to aquatic organisms and beneficial arthropods; therefore, based on the assessment of the potential risk to these organisms from short-term exposure, label statements regarding these hazards and risk mitigation measures are required.

Value Considerations

What Is the Value of Timorex Gold?

Timorex Gold is a non-conventional fungicide that can be used in both conventional and organic production systems.

Timorex Gold has demonstrated effectiveness in controlling or suppressing powdery mildew, downy mildew, and late blight on registered crops. The inclusion of tea tree oil in a conventional spray program could reduce the reliance on chemical fungicides. Timorex Gold also provides a non-conventional option for organic production. The multi-site mode of action of tea tree oil reduces the potential for resistance development.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Timorex Gold to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

The label for the technical grade active ingredient includes the hazard signal words, "CAUTION POISON", "DANGER – EYE IRRITANT", "DANGER – SKIN IRRITANT", and "POTENTIAL SKIN SENSITIZER". Additional precautionary statements include "Harmful if swallowed. Severely irritating to the eyes, skin and respiratory tract. DO NOT get in eyes, on skin or clothing, or inhale sprays, mists or vapours. Potential skin sensitizer."

The label for the commercial end-use product also includes hazard signal words and precautionary statements to identify the hazards and minimize human health risks. The following hazard signal words are included on the label for Timorex Gold: "WARNING - EYE IRRITANT", "WARNING – SKIN IRRITANT", and "POTENTIAL SKIN SENSITIZER", and the following precautionary statements are included on the label: "Causes eye, skin, and mucous membrane irritation. DO NOT get in eyes, on skin or clothing, or inhale sprays, mists or vapours." and "Potential skin sensitizer."

To prevent skin, eye, and respiratory tract occupational exposures and risks from tea tree oil, the label for Timorex Gold contains the following personal protective equipment (PPE) statements: "Workers potentially exposed to the product through mixing, loading, applying, and clean-up and repair activities must wear chemical-resistant goggles or a face shield, an appropriate NIOSH-approved respirator, a long-sleeved shirt and long pants, chemical-resistant gloves and shoes plus socks. Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions are available for washables, use detergent and hot water. Keep and wash PPE separately from other laundry."

Risks from potential occupational exposures to tea tree oil are further mitigated by occupational hygiene statements on the label for Timorex Gold including "Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet. Remove clothing immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing. Remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing."

"A restricted-entry interval (REI) of 4 hours must be observed following application. Do not enter or allow worker entry into treated areas during the REI.", "For greenhouse applications, vents should be opened and ventilation fans should be operational during the REI.", and "Treated

crops should not be harvested until a pre-harvest interval (PHI) of two days has passed." are additional risk mitigation measures that are included in the application directions on the label for the end-use product.

To avoid inadvertent bystander exposure during application, the Timorex Gold label includes the statements, "Keep unprotected persons out of the areas of the greenhouse to be treated for the duration of the treatment and the restricted-entry interval (REI).", "Do not apply to field crops when bystanders are in the vicinity of the fields to be treated.", and "Apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools, and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment, and sprayer settings."

Environment

Label statements indicating toxicity to aquatic organisms and beneficial arthropods are required. To minimize potential risks to aquatic organisms, buffer zone label statements for the protection of aquatic environments are also required.

Next Steps

Before making a final registration decision on tea tree oil, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on tea tree oil (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Tea Tree Oil

The original detailed review for Tea Tree Oil Technical and Timorex Gold can be found in Evaluation Report ERC2014-01, *Tea Tree Oil*.

1.0 The Active Ingredient, Its Properties and Uses

Please refer to ERC2014-01 for a review of the chemistry for the active ingredient and end-use product.

1.1 Directions for Use

Timorex Gold is applied to foliage as a 0.5–1.0% solution using ground application equipment. Re-application occurs at 7–14 day intervals. The shorter application interval is intended for use under conditions that promote rapid disease development. The higher rate should be used when disease pressure is high. Good coverage and wetting of the foliage is required. The spray solution should completely penetrate the leaf canopy and cover both the top and underside of all leaves.

1.2 Mode of Action

Please refer to ERC2014-01 for details on the mode of action of tea tree oil.

2.0 Methods of Analysis

Please refer to ERC2014-01 for a review of the methods of analysis for the active ingredient and end-use product.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Please refer to ERC2014-01 for a summary of toxicology.

ERC2014-01 included a summary of a registrant submitted data waiver rationale requesting that the developmental toxicity information requirements be addressed by information from a published study of the developmental toxicity of a component of tea tree oil, α-terpinene, combined with published information illustrating the similarity of the metabolism of the major components of tea tree oil. While this was accepted under the original conditional registrations of the technical grade active ingredient, Tea Tree Oil Technical, and the end-use product, Timorex Gold, one of the conditional data requirements was the submission of a prenatal developmental toxicity study of whole tea tree oil previously submitted to the United States Environmental Protection Agency. To address this data requirement, the registrant submitted a developmental toxicity study of tea tree oil conducted in rats and this study is summarized below.

In the submitted developmental toxicity study, tea tree oil was administered by gavage to pregnant female rats at dose levels of 0, 75, 150, and 300 mg/kg bw/day on gestation days 5–19. Doses were reduced to 0, 30, 60, and 120 mg/kg bw/day early in the study because of the death of a high dose dam and clinical signs observed in animals in the two highest dose groups. The maternal lowest-observed-adverse-effect-level (LOAEL) was 60 mg/kg bw/day based on reduced body weight gains and food intake at the two highest dose levels. The maternal no-observed-adverse-effect-level (NOAEL) was 30 mg/kg bw/day. The developmental LOAEL was 120 mg/kg bw/day based on reduced fetal body weights and the developmental NOAEL was 60 mg/kg bw/day.

This study provides clarification on the potential developmental effects of whole tea tree oil compared to the previously submitted study on a component, α-terpinene, which constitutes only 5–13% of the oil which were reviewed under the initial registration. The results of the study do not change the existing toxicity profile for tea tree oil. Details on the developmental toxicity study are provided in Appendix I, Table 1.

Incident Reports

As of 17 February 2016, the PMRA had received one domestic animal incident report involving the active ingredient, tea tree oil. This incident also involved other active ingredients. This same incident report was reviewed for the previous assessment of tea tree oil. Please refer to ERC2014-01 for a summary of the review of that incident report.

3.2 Occupational and Residential Risk Assessment

3.2.1 Dermal Absorption

The registrant submitted a published in vitro skin penetration of tea tree oil for the previous conditional registration of Tea Tree Oil Technical and Timorex Gold. Based on the recovery of terpinen-4-ol and α-terpineol, the average absorption of neat tea tree oil across human donor epidermal membranes in vitro was 2.83% with absorption as high as 4.13% for epidermal membranes from a single donor. A 20% dilution of tea tree oil in ethanol reduced the average absorption to 1.45% and partial occlusion of the epidermal membranes increased the average absorption to 7.08%. There is likely to be a range of absorption potentials for tea tree oil components as some have high water solubility and low lipid solubility, while others have low water solubility and high lipid solubility.

3.2.2 Use Description

The end-use product Timorex Gold is currently registered for controlling or suppressing a range of fungal infections (in other words, powdery mildew, downy mildew, late blight, grey mold) on grapes, greenhouse tomatoes, greenhouse and open field peppers, greenhouse cucumbers, strawberries, blueberries, raspberries, and potatoes. Timorex Gold is to be applied by airblast and with conventional spray equipment (for example, groundboom, high pressure and knapsack sprayers). The end-use product is diluted with water – from 2.0–12.0 L/ha diluted in 400–1200 L spray volume for control of powdery mildew in greenhouse tomato to 3.0–15.0 L/ha diluted in 600–1500 spray volume for the suppression of downy mildew on grapes. Enough spray solution

is applied to penetrate the leaf canopy and cover the tops and undersides of all leaves. Application intervals are 7–14 days for preventative treatments.

3.2.3 Mixer, Loader, and Applicator Exposure and Risk

Please refer to ERC2014-01 for a summary of mixer, loader and applicator exposure and risk.

3.2.4 Postapplication Exposure and Risk

Please refer to ERC2014-01 for a summary of postapplication exposure and risk.

3.2.5 Residential and Bystander Exposure and Risk

Please refer to ERC2014-01 for a summary of residential and bystander exposure and risk from tea tree oil.

3.3 Food Residue Exposure Assessment

3.3.1 Food and Drinking Water

Please refer to ERC2014-01 for a summary of food and drinking water exposure and risk.

One of the conditions of registration of Timorex Gold included in ERC2014-01 was a requirement that the registrant submit "information to characterize the metabolic pathways of the major components of tea tree oil and whether residues of the major components and their metabolites are present on treated crops after the administration of Timorex Gold." In response to this requirement, the registrant submitted a waiver rationale which is summarized below.

The waiver rationale is based on the premise that the tea tree oil components selected for analysis in submitted crop residue studies, terpinen-4-ol, γ-terpinene, and 1,8-cineole, are the three highest concentration components and are expected to have the worst case potential for being present in any residues on crops treated with Timorex Gold. To support this, the registrant noted that according to an International Standards Organization quality standard for tea tree oil (ISO/FDIS 4730:2004), terpinen-4-ol, γ-terpinene, and 1,8-cineole are the highest concentration components of the oil. Also, although all tea tree oil components are volatile, terpinen-4-ol and γ-terpinene have the lowest vapour pressures. Therefore, it is reasonable to assume that these two compounds are likely to be present in any tea tree oil residues on treated crops. This is also supported by the fact that although terpinen-4-ol, γ-terpinene, and 1,8-cineole were measured in submitted crop residue studies, the component detected was terpinen-4-ol, and it was only detected when a product containing a higher concentration of tea tree oil than Timorex Gold was used on crops at higher application rates. Based on the results of degradation/stability studies of tea tree oil in cosmetic products, the oil is likely to be reasonably stable in a pesticide formulation that is diluted in water. It was noted that as tea tree oil oxidizes, the α-terpinene, γ-terpinene, and α-terpineolene concentrations decrease and the ρ-cymene concentration increases. This is not likely to impact on potential crop residues as ρ-cymene is one of the most volatile tea tree oil components and it is present at lower starting concentrations in tea tree oil than terpinen-4-ol or γ-terpinene. Other oxidation products such as 1,2,4-trihydroxymenthane are difficult to

measure, are present in lower concentrations, and as a result, they may be undetectable in crop residues when formulations such as Timorex Gold are diluted in water and applied to crops. Finally, in published analytical studies, major tea tree oil components (for example, ρ-cymene, terpinen-4-ol, α-terpinene, etc...) have been identified in a range of fruits, vegetables, and spices including crops on the label for Timorex Gold. Therefore, it is likely that there are existing background levels of these compounds in the human diet.

This waiver rationale was considered to be acceptable and addresses the requirement for information on whether residues of the major components of tea tree oil and their metabolites are likely to be present on crops treated with Timorex Gold.

3.3.2 Maximum Residue Limits

Please refer to ERC2014-01 for a summary of information on maximum residue limits.

4.0 Impact on the Environment

Please refer to ERC2014-01 for a summary of the environmental fate and behaviour as well as the environmental risk characterization of tea tree oil.

5.0 Value

Please refer to ERC2014-01 for a summary of the full review of all use claims.

5.1 Consideration of Benefits

Tea tree oil is a non-conventional fungicide that can be used in rotation with conventional fungicides or can be integrated into organic production systems. The inclusion of tea tree oil in a conventional spray program could reduce the reliance on chemical fungicides.

The mode of action is not completely understood; however, tea tree oil contains multiple organic compounds that can influence the success of pathogen establishment and growth. This multi-site mode of action reduces the potential for resistance development.

Downy mildew is a highly destructive disease of grapevines in all grape-growing areas of the world. It causes fruit rot, uneven fruit maturity, reduced sugar content, and reduced plant vigour. New products are required for both conventional integrated pest management (IPM) and organic production systems.

5.2 Effectiveness Against Pests

5.2.1 Suppression of Downy Mildew (*Plasmopara viticola*) on Grape

Three efficacy trials conducted in Israel and in Canada in 2007 and 2008 were reviewed to support the claim of suppression of downy mildew (*Plasmopara viticola*) on grape. Based on the performance of tea tree oil in the trials, the weight of evidence shows that tea tree oil will suppress downy mildew on grape when applied using the proposed use pattern.

Review results for the remaining claims can be found in ERC2014-01.

5.3 Non-Safety Adverse Effects

Phytotoxic effects observed in trials were attributed to incorrect application. The label includes a recommendation to test the product on a small number of plants for sensitivity before applying on a commercial scale.

5.4 Supported Uses

The reviewed value information was sufficient to support the claim. Details of all supported uses are provided in Appendix I, Table 3.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

Tea tree oil technical and the end-use product, Timorex Gold, were previously assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria in ERC2014-01.

6.2 Formulants and Contaminants of Health or Environmental Concern

Formulants or contaminants of Health or Environmental Concern were assessed in ERC2014-01.

7.0 Summary

7.1 Human Health and Safety

Please refer to ERC2014-01 for a summary of human health and safety.

A study of the developmental toxicity of tea tree oil submitted in response to one of the data requirements of the previous conditional registration of tea tree oil provides clarification on the potential developmental effects of whole oil compared to a previously submitted study on a single component, α-terpinene. The results of the study do not appreciably alter the existing toxicity profile for tea tree oil, which were reviewed under the initial registration.

An additional data requirement of the previous conditional registration of tea tree oil included information on whether residues of the major components of tea tree oil and their metabolites are present on treated crops after the application of Timorex Gold. The registrant submitted a data waiver rationale for this information that was accepted by the PMRA. Based on the submitted information, it is expected that the tea tree oil components already analyzed for in crop residue studies, terpinen-4-ol, γ-terpinene, and 1,8-cineole, have the greatest potential for being present in any tea tree oil residues on crops following the application of the end-use product. In

[5] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

previously submitted and reviewed residue studies, levels of these tea tree oil components on treated crops were less than the limit of quantification 48 hours after application of the end-use product.

7.2 Environmental Risk

Please refer to ERC2014-01 for a summary of environmental risk.

7.3 Value

As a non-conventional fungicide, Timorex Gold can be used in organic production to manage important diseases. This product can also be used in conventional production systems, which could reduce the reliance on chemical fungicides and aid in resistance management. The mode of action provides control or suppression of a variety of fungi and reduces the risk of resistance development.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Tea Tree Oil Technical and Timorex Gold, containing the technical grade active ingredient tea tree oil, to control powdery mildew on greenhouse pepper, tomato, cucumber and grape, suppress powdery mildew on strawberry, suppress downy mildew on grape and greenhouse cucumber, and suppress late blight on greenhouse tomato.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

♀	female
↓	decrease
bw	body weight
ERC	evaluation report
GD	gestation day
ha	hectare(s)
IPM	Integrated pest management
ISO-FDIS	International Organization for Standardization – Final Draft International Standards
kg	kilogram
L	litre
LOAEL	lowest observed adverse effect level
M	Multi-site (mode of action)
mg	milligram
NC	Not classified
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no observed adverse effect level
PHI	preharvest interval
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
REI	restricted entry interval

Appendix I Tables and Figures

Table 1 Prenatal Developmental Toxicity of Tea Tree Oil

Study	Species/Strain Doses	Result	Target Organ/Significant Effects/Comments	Reference
Prenatal Developmental Toxicity	Rat/Wistar – HsdHan: WIST 24 ♀(pregnant)/dose 0 (peanut oil), 75, 150, 300 mg/kg bw/day by gavage on GD 5–7 0, 30, 60, 120 mg/kg bw/day by gavage for remainder of study (that is, to GD 19)[a]	Maternal: NOAEL = 30 mg/kg bw/day LOAEL = 60 mg/kg bw/day Developmental: NOAEL = 60 mg/kg bw/day LOAEL = 120 mg/kg bw/day	Maternal: Effects a LOAEL: ↓ body weight gain, ↓ food consumption Developmental: Effects at LOAEL: ↓ fetal body weight	2499299

[a] Doses were reduced early in the study due to the death of one high dose dam and treatment related clinical signs in dams from the two highest dose groups.

Table 2 Registered Alternatives Based on Mode of Action (as of July 2015)

Crop	Disease (pathogen)	Registered Mode of Action Groups
Grape	downy mildew (*Plasmopara viticola*)	M, 3, 7+11, 33, 40, 43, 45, NC
	powdery mildew (*Erysiphe necator*)	M, 3, 7, 7+9, 7+11, 11, 13, 44, U, NC
Greenhouse tomato	powdery mildew (*Oidium neolycopersici, O. lycopersici, Leveillula taurica*)	M, 3, 7+11, 9+12, NC
	late blight (*Phytophthora infestans*)	NC
Greenhouse pepper	powdery mildew (*Leveillula taurica*)	M, 3, 7+11, 9+12, 44, NC
Greenhouse cucumber	powdery mildew (*Podosphaera xanthii*)	3, 7+11, 9+12, 44, NC
	downy mildew (*Pseudoperonospora cubensis*)	9, NC
Strawberry	powdery mildew (*Podosphaera aphanis*)	M, 3, 7, 7+11, 11, 13, 12, NC

Table 3 List of Supported Uses

Crop	Supported use claim
Grape	Suppression of downy mildew (*Plasmopara viticola*) at rates of 3–15 L/ha applied on a 7–14 day interval. Use the shorter application interval under conditions that promote rapid disease development. Use the higher rate when disease pressure is high.
	Control of powdery mildew (*Erysiphe necator*) at the rates of 1.5–2.0 L/ha.
Greenhouse Tomato	Control of powdery mildew (*Oidium neolycopersici, O. lycopersici* or *Leveillula taurica*) at the rates of 2–12 L/ha.
	Suppression of late blight (*Phytophthora infestans*) at the rates of 2–12 L/ha.
Greenhouse Pepper	Control of powdery mildew (*Leveillula taurica*) at the rates of 1–1.5 L/ha.

Crop	Supported use claim
Greenhouse Cucumber	Control of powdery mildew (*Sphaerotheca fuliginea* or *Erysiphe cichoracearum*) at the rates of 2–8 L/ha.
	Suppression of downy mildew (*Pseudoperonospora cubensis*) at the rates of 2–8 L/ha.
Strawberry	Control of powdery mildew (*Podosphaera aphanis* syn. *Sphaerotheca macularis*) on strawberry at the rates of 2–8 L/ha.

References

A. List of Studies/Information Submitted by Registrant

1.0 Human and Animal Health

PMRA Document Number	Reference
1745020	Cross, S.E., M. Russell, I. Southwell and M.S. Roberts. 2007. Human Skin Penetration of the Major Components of Australian Tea Tree Oil Applied in its Pure Form and as a 20% Solution in vitro. European Journal of Pharmaceutics and Biopharmaceutics, 69(2008): 214-222. DACO: 4.8 (USEPA)
2499299	2012, Prenatal Development Toxicity, DACO: 4.5.2
2499301	2015, Metabolism/Toxicokinetics Studies (Nature of Residue), DACO: 6.3

2.0 Value

PMRA Document Number	Reference
2544986	2015, Timorex Gold grape DM claims, DACO: 10.2.3.1
2544987	2015, Control of downy mildew caused by *Plasmopara viticola* in table grapes - Petachiya No. 7, DACO: 10.2.3.3
2544988	2015, Control of downy mildew caused by *Plasmopara viticola* in table grapes - Harel No. 7, DACO: 10.2.3.3
2544989	2007, Fungicides for control of grapevine downy mildew, 2008, DACO: 10.2.3.3
1745089	2008, Mode of antifungal activity of the essential tea tree oil in the control of banana black sigatoka and other diseases and crops, DACO: 10.2.1
1745090	2000, The mode of antimicrobial action of the essential oil of *Melaleuca alternifolia* (tea tree oil), DACO: 10.2.1
1745097	2004, Control of plant diseases by tea tree oil, DACO: 10.2.3.2
1745098	2006, *Melaleuca alternifolia* (Tea Tree Oil): a review of antimicrobial and other medicinal properties, DACO: 10.2.3.2
1843850	2009, Notes and rationales on labeled pests, DACO: M10.1, M10.2, M10.2.2